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Full name, address and postcode of the or of each applicant *(underline all surnames)*
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Patents ADP number *(if you know it)* 05838123004

If the applicant is a corporate body, give the country/state of its incorporation
United Kingdom

Title of the invention
Synthesis of 3 hydroxy - 5β - steroids

Name of your agent *(if you have one)*
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# Synthesis of 3 hydroxy-5β-steroids

The present invention relates to the synthesis of 3-hydroxy-5β-steroids.

It has been shown that steroids possessing a 5β-hydrogen have utility in the treatment of cognitive dysfunction (WO 01/49703, WO 02/079221, WO 01/23406). The present invention has been made in the synthesis of said 5β steroids, and in the synthesis of 3-hydroxy-5β-steroids generally. The present invention enables such steroids to be prepared with improved efficiency and with controllable stereospecificity as between the 3α and 3β isomers.

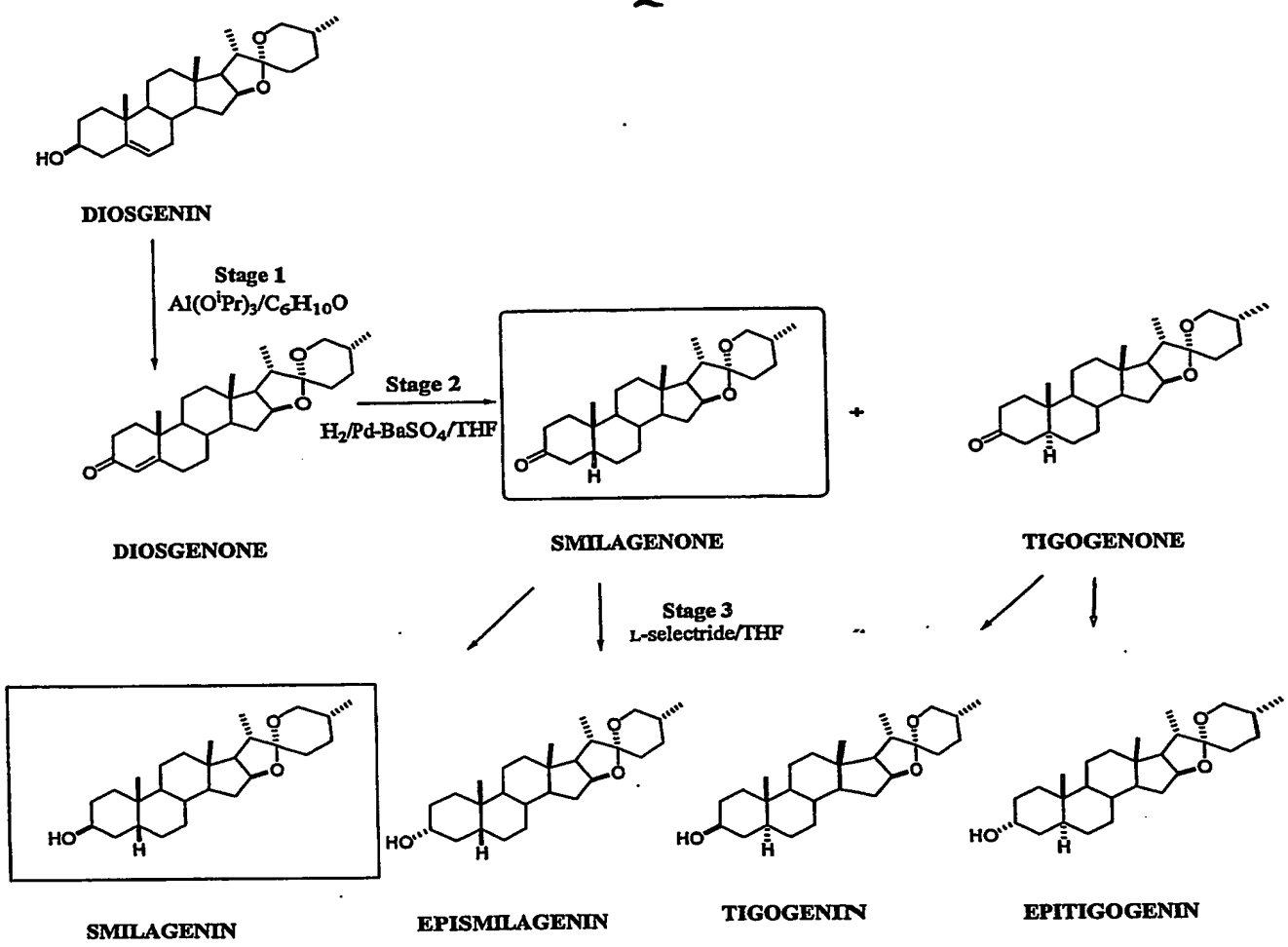
According to a first aspect of the present invention, there is provided a method of preparing 3-hydroxy steroids, which comprises reducing a 3-keto steroid using as reducing agent a selectride or an aluminium hydride. Generally speaking, the selectride reducing agent produces predominantly 3β hydroxy steroids (e.g. smilagenin and the like), and the aluminium hydride produces predominantly 3α steroids (e.g. epismilagenin and the like).

The term "selectride" means any alkali metal tri-alkyl or tri-aryl borohydride reducing agents such as lithium tri(sec-butyl) borohydride, lithium tris-amyl borohydride or lithium triphenyl borohydride, or the corresponding reducing agents with lithium replaced by potassium. Alkyl groups preferably contain from 1 to 7 carbon atoms. Aryl groups preferably contain from 6 to 12 carbon atoms and may be alkyl-substituted.

The term "aluminium hydride" means any reducing agent containing aluminium and hydride moieities, optionally with other moieties such as lithium or organic groups (e.g. alkyl or alkoxy, suitably containing from 1 to 7 carbon atoms) also present, such as lithium aluminium hydride (lithal), dibutyl aluminium hydride or lithium aluminium t-butoxy hydride.

The said reduction is described in more detail, without limitation and purely by way of illustration, as Stage 3 of the overall process described below.

More particularly, but not exclusively,we have developed a process for the synthesis of either smilagenin and epismilagenin from diosgenin utilising selective reductions to control stereochemistry. Scheme 1 shows the process as developed for the synthesis of smilagenin, utilising an oxidation to afford the αβ-unsaturated ketone, diosgenone, followed by catalytic reduction to introduce stereoselectively the 5β-hydrogen followed by selective hydride reduction to introduce the 3β-hydroxyl group stereoselectively. The direct reduction of diosgenin using palladium on carbon as a catalyst gives predominantly the 5α-product, tigogenin.




**Scheme 1: Manufacturing route for smilagenin from diosgenin**

## Details of Stage 1

Stage 1 of the synthetic route utilises a modified Oppenauer reaction (R. V. Oppenauer, *Rec Trav. Chim.* **56**, 137 (1937). This reaction is the aluminium alkoxide catalysed oxidation of a secondary alcohol to the corresponding ketone.

Whilst the oxidation of diosgenin to diosgenone has been described in the literature, practica considerations have prevented the process being of much utility. It has been discovered by the applicant that the use of 0.5 equivalents of aluminium isopropoxide in a combination of 5 volumes of 2-butanone and 5 volumes of toluene with the reaction heated to between 60°C and the reflux temperature of the solvent effected oxidation of diosgenin in a timely manner Aluminium salts are removed by dissolution in 1M hydrochloric acid. The use of toluene a a co-solvent aids in the isolation, after acid work–up, of the product, diosgenone, in typicall 55-70% yield as a clean product.

Marker et al (Marker *et al.*, 1940) described the oxidation of diosgenin by the method o Oppenauer, using cyclohexanone and aluminium *iso*-propoxide (5 equiv.) in toluene. Th reaction was very dilute (58 volumes; excluding work-ups) and is impractical for economi processing on a large-scale. The use of a large excess of aluminium *iso*-propoxide is no desirable, since this will lead to an increased effluent burden. Irismetov has also describe the oxidation by diosgenin by the method of Oppenauer, using cyclohexanone and aluminiur

*iso*-propoxide (1 equiv.) in toluene (Irismetov & Goryaev, 1981). Again this process suffers from low dilution, though the amount of aluminium *iso*-propoxide has been reduced to the stoichiometric amount. Djerrasi has reviewed the Oppenauer oxidation (Djerassi, 1951). The introduction of the combination of cyclohexanone and toluene (or xylene) provided significantly shorter reaction times when compared to the use of acetone and benzene in the original work of Oppenauer. Cyclohexanone has found particular use in the field of steroids since it can be removed from the product by steam distillation. Djerrasi stated that 2-butanone has found utility though it generally does not offer advantages over acetone or cyclohexanone. The use of 1-3 equivalents of aluminium *iso*-propoxide were typically used.

It is surprising that the use of sub-stoichiometric amounts of aluminium *iso*-propoxide in conjunction with 2-butanone and toluene as reaction solvent affords a similar yield of diosgenone in a similar timeframe to the use of cyclohexanone and stoichiometric amounts of aluminium *iso*-propoxide.

The present method provides cost savings on reagents and disposal charges. 2-Butanone has a lower boiling point than cyclohexanone (80°C *cf.* 154-156°C) and is therefore easier to remove from the reaction mixture.

## Details of Stage 2

Stage 2 of the manufacturing method for smilagenin (Scheme 1) utilises the reduction of the double bond of the αβ-unsaturated carbonyl. To effect the desired β-face attack of hydrogen, a number of catalysts and conditions were screened. Initial work investigated the method as described in the literature wherein the reduction is effected by hydrogen at 1 bar in the presence of 10% palladium on carbon and 20% potassium hydroxide in methanol as solvent. Whilst this effected the desired selectivity (5β:5α = 93:7), and was of commercial utility, the avoidance of alkali would afford simpler work-up conditions. Marker has shown that the reduction of diosgenone to smilagenone can be achieved with palladium-barium sulphate catalyst in diethyl ether solution under hydrogen (*i.e.* 10 psi). The low concentration (500 volumes; normal processing volumes are in the range of 5-30 volumes) and high catalyst loading (1000%; normal catalyst loadings are in the range 1-20%) render the process as described unfeasible and uneconomical for large-scale work. An additional consideration is that diethyl ether is unsuitable for large-scale work for safety reasons. Table 1 details the various conditions investigated for the reduction using palladium on barium sulphate as the catalyst.

Other workers have also investigated the reduction of diosgenone to smilagenone. Djerassi reduced diosgenone in ethanol (450 ml) over pre-reduced 10% Pd-C (0.8 g) at atmospheric pressure. Crude smilagenone was isolated by precipitation with water and recrystallised from chloroform/methanol to furnish pure smilagenone (7.2 g, 72%) with a melting point of 179-183°C. The yield was not changed when the reaction was carried out in the presence of potassium hydroxide (3 g). An analytically pure sample melted at 186-188°C (Djerassi *et al.*, 1952).

In the pregnane series Suvorov has found that pyridine has a marked effect upon the outcome of such hydrogenation reactions. Typically, in this work the catalyst of choice was 10% palladium on calcium carbonate (Pd-$CaCO_3$). In such cases the selectivity was found to be markedly superior to those reactions run in alcoholic solvents, even with the addition of caustic (Suvorov & Yaroslavtseva, 1961). The work-up employed in this study involved quenching onto dilute hydrochloric acid and extraction of the product into chloroform. The organic extract was washed with dilute hydrochloric acid, 8% aqueous sodium bicarbonate solution and water until neutral to litmus. Such methods lead to the production of large

amounts of aqueous containing pyridine and halogenated solvents effluent that require disposal, adding to the cost of processing.

Irismetov demonstrated that high selectivity could be achieved in the reduction of diosgenone to smilagenone. In this work diosgenone (1 g) was hydrogenated over 5% Pd-$CaCO_3$ (1 g) in pyridine (30 ml) at atmospheric pressure. After filtration to remove the catalyst and solvent evaporation the residue was crystallised from alcohol to afford a solid melting at 209-211°C. No yield is given (Irismetov & Goryaev, 1981). For large-scale production this work suffers from high catalyst loadings (100%) and moderately dilute solutions. Pyridine is a noxious solvent and is more generally used in stoichiometric amounts as an acid scavenger in large-scale work. The requirement to evaporate to dryness is not preferred on large-scale.

US patent 736,818 makes a claim for the reduction of 3-keto-$\Delta^4$-steroids to 5β-H steroids with a palladium catalyst, in the presence of an inorganic base and in an anhydrous medium. The preferred solvent is methanol and the preferred base is potassium hydroxide. Diosgenone is not exemplified. We find that diosgenone is poorly soluble in alcohols (specifically ethanol), which would render this process very dilute. Such a method also requires an extractive work-up procedure.

US patent 763,301 makes reference to the utility of alkali (*i.e.* sodium or potassium hydroxide) in increasing the amount of 5β-H product in the reduction of 3-keto-$\Delta^4$-steroids. This patent makes a specific claim for the utility of triethylamine in this context. Of the solvents chosen ethanol, ether, ethyl acetate and methylcyclohexane are cited, with 1,4-dioxane being the preferred solvent.

Table 1: Solvent screening studies with Pd-$BaSO_4$

| Entry | Time / h | Vol | Solvent | Yield / % | Smilagenone | Tigogenone | Diosgenone | Tigogen |
|---|---|---|---|---|---|---|---|---|
| 1 | 4 | 5 | THF | 100 | 95.7 | 2.1 | <0.1 | 1.2 |
| 2 | 12 | 20 | $Et_2O$ | 51 | 86.5 | 3.7 | 7.3 | 1.5 |
| 3 | 15 | 15 | TBME | 43 | 91.1 | 7.6 | 0.3 | 1.0 |
| 4 | 7 | 15 | DEM | 54 | 91.1 | 6.5 | 0 | 2.2 |
| 5 | 16 | 10 | 1,4-dioxan | 94 | 95.7 | 2.9 | - | 1.4 |
| 6 | 7 | 15 | IPA | 16 | 67 | 26.1 | 0.5 | 4.8 |
| 7 | 4 | 15 | EtOAc | 70 | 93.2 | 4.2 | 0.4 | 1.8 |
| 8 | 7 | 15 | Acetone | 28 | 82.6 | 13.0 | 0.5 | 3.7 |
| 9 | 6 | 15 | MIBK | 79 | 92.4 | 13.0 | 1.5 | 1.6 |
| 10 | 3 | 15 | cyclohexane | 52 | 92.6 | 6.7 | - | 0.7 |
| 11 | 10 | 5 | Toluene | 100 | 92.1 | 2.5 | 4.6 | 0.8 |
| 12[1] | | 15 | NMP | 100 | 72 | 9.0 | 17.5 | 1.1 |
| 13[1] | 2 | 5 | THF | 100 | 95.7 | 2.1 | <0.1 | 1.2 |
| 14[1] | 2 | 5/1 | THF/20% pyridine | | | | | |

**Note: 1. the catalyst was from Alfa**

Initial method development work examined two solvents in the hydrogenation reaction, namely ethanol and tetrahydrofuran (THF). The latter solvent became the solvent of choice since it offered an improved solubility of diosgenone, resulting in a higher throughput process, and provided a simple work-up when compared to the ethanol/aqueous sodium hydroxide system. The work-up consisted of concentration of the reaction mixture and purification by reslurrying the residue. A number of solvents were effective in achieving partial purification of the smilagenone. Surprisingly, later work demonstrated the ability to telescope stages 2 and 3 by removing the catalyst by filtration and reduction of the solution of smilagenone in THF with L-selectride to furnish smilagenin. It was demonstrated that the impurities formed in the process (epitigogenin) could be readily removed at this stage.

The goals of the solvent screening work were to see if other solvents offered process advantages over THF in terms of selectivity, concentration and general processing characteristics. A diverse range of solvents was selected and screened on a 5 g scale under 1 atmosphere of hydrogen at ambient temperature. Each reaction used a 20% loading of 5% Pd-$BaSO_4$ (r) purchased from Sigma-Aldrich unless otherwise stated. For those reactions that required 15 volumes or more of solvent not all of the diosgenone was fully dissolved and the reaction was carried out on the resultant suspension. The results of this study are recorded in table 1. The filter cake from these reactions was washed well with dichloromethane (DCM) to ensure that a complete mass balance was achieved. The results of this study are recorded in table 2.

**Table 2: Product recovery from Celite filter cake**

| Entry | Ref. | Solvent | Yield/% | Smilagenone | Tigogenone | Diosgenone | Tigogenin |
|---|---|---|---|---|---|---|---|
| 1 | KST/99 | $Et_2O$ | 27 | 93.7 | 0.4 | 5.5 | 0.3 |
| 2 | KST/101 | TBME | 55 | 99.0 | 0.7 | 0.3 | - |
| 3 | CRW031 | IPA | 72 | 93.6 | 0.6 | 4.7 | 0.8 |
| 4 | CRW032 | EtOAc | 24 | 99.0 | 0.2 | 0.7 | 0 |
| 5 | CRW029 | acetone | 67 | 97.2 | 0.3 | 2.0 | 0.4 |
| 7 | KST/102 | MIBK | 17 | 96.3 | 0.3 | 2.8 | 0.3 |
| 8 | KST/103 | Cyclohexane | 41 | 99.0 | 0.3 | 0.2 | - |

Other conditions and catalysts were screened in order to investigate whether improvements in selectivity could be achieved. From Table 3 it is apparent that an increase in pressure to 2 bar resulted in a lower selectivity for the process. The use of the unreduced form of Pd-BaSO4 also gave lower selectivity. The use of Pd-$CaCO_3$ in THF also gave a useful process; the selectivity of which could be further improved by using pyridine as solvent (Suvorov & Yaroslavtseva, 1961). The latter reaction was worked up by quenching onto dilute hydrochloride acid, filtration of the resultant precipitate and washing with water to furnish smilagenone in 80% yield. Overall, this does not represent a superior process to that using THF for large-scale manufacture due to the increased processing required. Surprisingly, the unreduced form of this catalyst was found to be less selective.

**Table 3: General screening studies**

| Entry | Scale/g | Solvent/Catalyst | Smilagenone | Tigogenone | Diosgenone | Tigogenin |
|---|---|---|---|---|---|---|
| 1 | 10 | Pd-$BaSO_4$/THF/2 bar | 87.8 | 7.3 | 1.8 | 1.5 |
| 2 | 100 | Pd-BaSO4 (u)/THF | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| 3 | 20 | Pd-$CaCO_3$ (r)/THF | 91.4 | 6.9 | - | 1.7 |
| 4 | | Pd-$CaCO_3$ (r)/pyridine | 94.7 | 2.6 | 0.8 | 1.5 |
| 5 | 20 | Pd-$CaCO_3$ (u)/THF | 81.1 | 14.2 | - | 1.7 |

Previously smilagenone had been purified by a reslurry in cyclohexane. During the development work MEK and IPA had also been found to be effective but were not further explored. The aim of this work was to examine purification of smilagenone by a formal recrystallisation from each of these solvents. From table 4 it is apparent that each of these solvents is able to raise the purity of smilagenone to >97%, with MEK being the most volume efficient.

**Table 4: Recrystallisation of crude smilagenone**

| Entry | Solvent | Volumes | Yield/% | Smilagenone | Ligogenone | Diosgenone | Yuccagenin |
|---|---|---|---|---|---|---|---|
| 1 | Input | - | | 91.35 | 5.15 | 1.71 | 1.27 |
| 2 | MEK | 5 | 70 | 97.77 | 1.20 | 0.39 | 0.51 |
| 3 | Cyclohexane | 8 | 72 | 97.71 | 1.10 | 0.33 | 0.57 |
| 4 | IPA | 12 | | 97.40 | 1.35 | 0.37 | 0.71 |

We have found that palladium on barium sulphate and palladium on calcium carbonate are particularly effective catalysts. It has been discovered that pre-reduced forms of the catalysts are superior to the unreduced forms.

THF and toluene have been found to be useful solvents for the reaction and give a similar selectivity to the use of pyridine as solvent. Both solvents are advantageous over pyridine as a process solvent on the basis of cost, work-up and disposal. The use of THF in particular has been shown to avoid the need for work-up and telescoping of the reaction mixture directly into stage 3 to furnish smilagenin of good purity. This avoids the need for work-up, isolation and drying of the intermediate smilagenone, providing savings in time and equipment usage and therefore expected improvements in manufacturing costs.

The use of the above catalysts in combination with THF or toluene represent a particularly useful combination, in the absence of any added base. Other replacement solvents for ether, such as *tert*-butyl methyl ether or diethoxymethane, are less efficient than THF due to the lower solubility of diosgenone in these solvents.

**Discussion of Stage 3**

Stage 3 of the overall scheme for the production of smilagenin from diosgenin required the selective production of the 3β-hydroxyl group. By contrast, if epismilagenin was to be produced a selective reduction to afford the 3α-hydroxyl functionality.

Marker (1940) effected the reduction of smilagenone to smilagenin by the Meerwein-Pondorff-Verly (MVP) method, though no yield was given.

Djerassi repeated the work of Marker to produce smilagenone by reduction of diosgenone. The smilagenone was subsequently reduced with LAH to afford almost exclusive formation of epismilagenin (Djerassi *et al.*, 1952)

Screening of reagents for this transformation indicates that L-selectride and other reagents in this family (e.g. K-selectride, LS-selectride and potassium triphenylborohydride) are effective in the reduction of smilagenone to smilagenin. These reagents not only have application only in the production of smilagenin, but other 3β-hydroxy-5β-steroids.

During the course of this work a number of reagents have been identified that lead to useful selectivity for the conversion of smilagenone into epismilagenin.

It has been discovered that either a 3α or 3β hydroxyl could be formed by the correct choice of hydride reducing agent. Whilst a number of reagents have been discovered to effect selectivity to either afford smilagenin or epismilagenin, two that have so far afforded the most utility are lithium tri-t-butoxyaluminium hydride to afford selectively the 3α-hydroxyl, e.g epismilagenin, and L-selectride (lithium tri-sec-butylborohydride) to selectively produce the 3β-hydroxyl e.g smilagenin. Table 5 lists reagents used in the reduction of smilagenone.

Table 5 Selectivity in the reduction of smilagenone.

| | Reagent | Temp. °C | Smilagenin | Epismilagenin |
|---|---|---|---|---|
| | DIBAL | | - | + |
| | Red-Al | | - | + |
| | Pt-C/$H_2$ | | - | + |
| | $LiAlH(O^tBu)_3$ | | - | + |
| | L-selectride | -78 | + | - |
| | L-selectride | -10 | + | - |
| | L-selectride | 25 | + | - |
| | L-selectride | -78 | + | - |
| | K-selectride | | + | - |
| | N-selectride | | + | - |
| | LS-selectride | | + | - |
| | KS-selectride | | + | |
| | | | | |
| | | | | |
| | | | | |
| | $KBH(Ph)_3$ | | + | - |
| | $AlH_3$ | 0 | - | + |
| | | | | |
| | | | | |
| | | | | |
| | | | | |

Note: Reactions performed in THF unless otherwise noted.

US patent 3,875,195 with a application priority date of 18th November 1972 in Germany, discloses the use of Raney-Nickel and hydrogen in a carboxylic acid solvent under high pressure for the preparation of 3β-hydroxy-5β-H-steroids.

Brown's paper (Brown et al, 1972) disclosing the use of L-selectride was published in the Journal of the American Chemical Society on 4th October 1972. The failure of the above workers to employ L-selectride provides evidence that this use of this reagent for this transformation is not obvious.

## EXAMPLES

***Example 1***

*Synthesis of diosgenone from diosgenin*

Diosgenin (1010 g, 2.44 mol), aluminium *iso*-propoxide (298.5 g, 1.05 mol, 0.44 equiv.) and butanone (5000 ml) were suspended in toluene (5000 ml, 5 volumes) and the reaction heated to reflux (88-90°C) for 7 hours.

A solution of 37% hydrochloric acid (1000 ml) in water (4000 ml) was added to the reaction mixture at 25-35°C and the mixture stirred for at least 30 minutes. The acidic aqueous phase is separated and re-extracted with toluene (2000 ml). The combined organic layers were washed with water (2 x 2000 ml) and evaporated to low volume at 50-75°C and 10-100 mbar, collecting ca. 8500 ml of distillate. Heptane (10,000 ml) was added over 40 minutes at 60-75°C. The slurry was held at 75°C for 40 minutes and cooled to –5 to 5°C and stirred for 3hours. The product was filtered off and washed with heptane (1000 ml) at 5°C. The product was oven dried at 40-60°C to afford diosgenone (728.6 g, 72%).

***Example 2***

*Synthesis of smilagenone from diosgenone*

Diosgenone (700 g) was dissolved in tetrahydrofuran (4500 ml) and purged with nitrogen. The mixture was treated with activated carbon (35 g) and hydrogenated over 5% $Pd/BaSO_4$ (reduced) (35 g) at 25°C, 2.5 barg hydrogen until hydrogen uptake ceased. The catalyst was filtered off.

The smilagenone can be isolated by concentration and precipitation by addition of water, or the solution can be processed into stage 3. 37 kg of diosgenone has been processed in two batches to provide after filtration of the catalyst and work-up by the aqueous drown-out method to furnish 34.4 kg (92% yield) smilagenone.

***Example 3***

*Synthesis of smilagenin from smilagenone*

Smilagenone (657 g) was dissolved in tetrahydrofuran (4000 ml) and the solution purged with nitrogen and cooled to provide an internal temperature of *ca.*-10°C. L-Selectride (2400 ml 1M in THF) was added over *ca.* 50 minutes and stirred for 90 minutes. A solution of citric acid (600 g) in water (2000 ml) was added slowly, maintaining the temperature below 0°C. The mixture was allowed to warm to ambient temperature and stirred for 30 minutes. The aqueous layer was separated and extracted with dichloromethane (2000 ml) and the layers separated. The aqueous layer was extracted with dichloromethane (1500 ml). The combined organic extracts were washed with water (4000 ml) and dried over $MgSO_4$. The organic extracts were evaporated to dryness to yield smilagenin.

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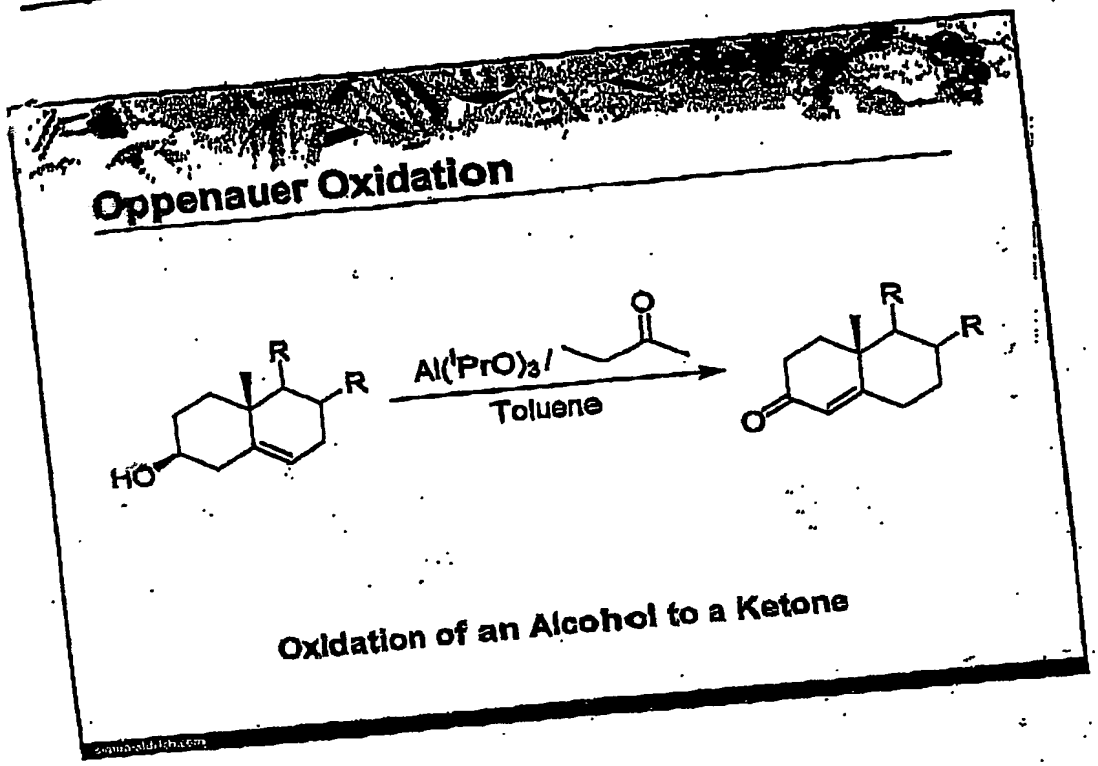
Stage 1


Oppenauer Oxidation
R
R
HO
Al(iPrO)3/
Toluene
O
R
R
O
Oxidation of an Alcohol to a Ketone

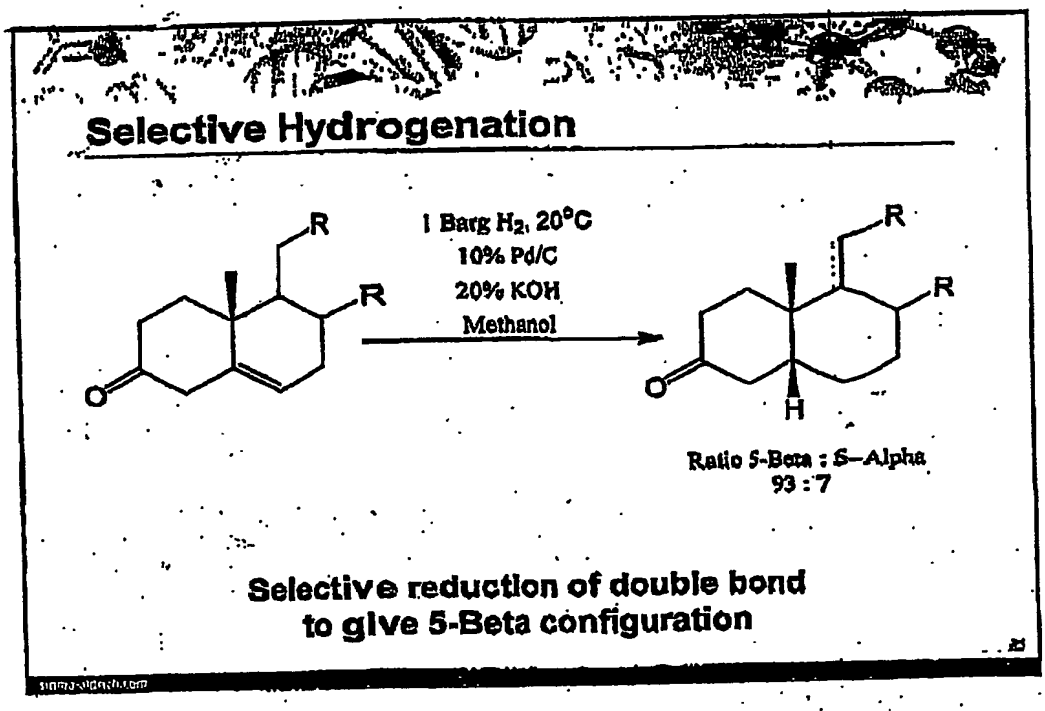
Stage 1 (continued) 2/8

## Oppenauer Oxidation

- Reaction is an equilibrium between the Alcohol and a Ketone used in excess as solvent. Ketone used in this case was 2-Butanone
- Toluene used as a co-solvent to aid isolation
- 0.5 equivalents Aluminium Isopropoxide needed - even though it is a catalyst
- Reaction took 6 hours at reflux - no ΔHr hazard
- 86% product formed with 3% SM & trace impurities
- Aluminium salts removed by dissolution in 1M HCl
- 60% isolated yield of clean product

3/8

Stage 2

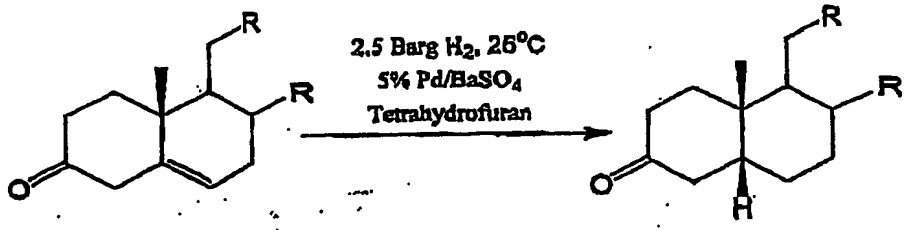

Selective Hydrogenation
R
R
O
1 Barg $H_2$, 20°C
10% Pd/C
20% KOH
Methanol
R
R
O
H
Ratio 5-Beta : 5--Alpha
93 : 7
Selective reduction of double bond
to give 5-Beta configuration

Stage 2 (continued) 4/8

## Selective Hydrogenation

- Conditions utilised were:-
  - 10% Pd/C catalyst (3% loading), 20% KOH solution
  - Ethanol as co-solvent
  - 1 Barg Hydrogen pressure at 20°C
- $\Delta H = -120\ kJ.mol^{-1}$ (CHETAH) $\Rightarrow$ Inherently Safe
- Isolated yield 85%. Ratio 5-Beta to 5-Alpha 93:7
- Key to selectivity is fast hydrogenation using Blazzi technology
- Isolated yield and isomer ratio exactly mimicked laboratory-scale (2L) results

## Selective Hydrogenation




Ratio 5-Beta : 5-Alpha
93 : 7

**Selective reduction of double bond to give 5-Beta configuration**

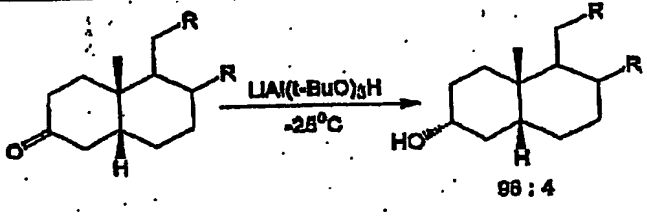
Stage 2 (continued) 5/8

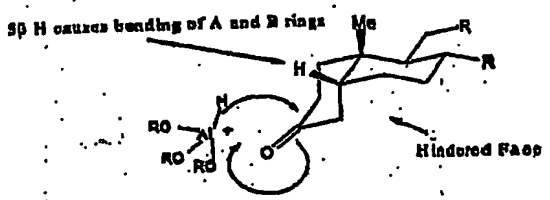
## Selective Hydrogenation

- Conditions utilised were:-
  - 5% Pd on $BaSO_4$
  - Tetrahydrofuran solvent
  - 2.5 Barg Hydrogen pressure at 25°C
- Conditions needed to be changed owing to lack of solubility of substrate in 2-phase KOH/Ethanol mix
- Same selectivity achieved as for other system (Ratio 5-Beta to 5-Alpha 93:7)
- Rapid hydrogenation using Blazzi again key to achieving selectivity

Stage 3

## Reduction Using $LiAl(t\text{-}BuO)_3H$



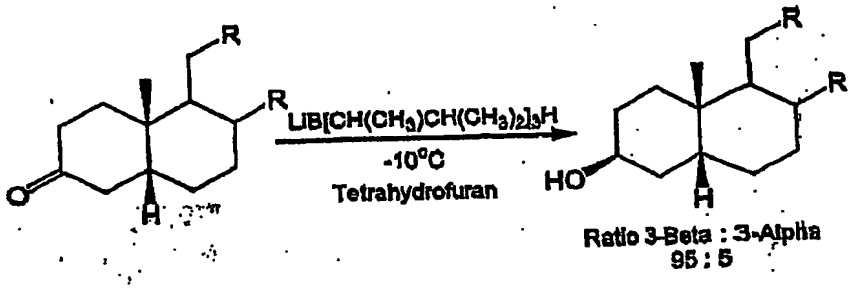

**Stereoselective reduction to 3-Alpha Hydroxy**
**Lower face is hindered, reagent delivers Hydride to top face**

Stage 3 (continued) 7/8

## Reduction using $LiAl(t\text{-}BuO)_3H$

- 1.1 equivalents Hydride employed. This reagent chosen to give selectivity
- Run at -25°C to further enhance selectivity
- $\Delta H$ = -130 kJ.mol$^{-1}$, $T_{ad}$ = ~50°C ⇒ Inherently Safe
- No Hydrogen evolved during the addition of Hydride (apart from that due to initial reaction with Water)
- Quench controlled using $Na_2SO_4$ solution (Exo + $H_2\uparrow$)
- Quench temperature critical to obtain filterable solid (Aluminium salts)
- Product precipitated by addition of Water (49-53%)
- Selectivity of desired 3-Alpha Hydroxy = 96:4

## Selective Reduction using Lithium Selectride




Ratio 3-Beta : 3-Alpha
95 : 5

Stereoselective reduction to 3-Beta Hydroxy
Lower face is hindered, reagent delivers Hydride to *lower* face

Stage 3 (continued)

## Selective Reduction using Lithium Selectride

- Selective reduction to give opposite configuration of the Alcohol from $LiAl(t\text{-}BuO)_3H$
- Reaction run in Tetrahydrofuran at −10°C
- Selectivity of 3-Beta to 3-Alpha of 95:5
- Work-up by quench into acid, acid washes, solvent extraction, further washes then solvent replacement
- Isolated yield: 80% of 90% pure material (~5% SM)
- Recrystallised to give 99% pure material

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